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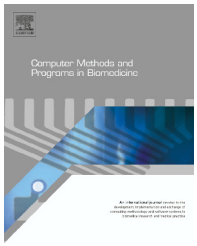

A data driven nonlinear stochastic model for blood glucose dynamics☆

Yan Zhang[a], Tim A. Holt[b], Natalia Khovanova[a,*]

[a] School of Engineering, University of Warwick, UK
[b] Department of Primary Care Health Sciences, Oxford University, UK

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ABSTRACT

The development of adequate mathematical models for blood glucose dynamics may improve early diagnosis and control of diabetes mellitus (DM). We have developed a stochastic nonlinear second order differential equation to describe the response of blood glucose concentration to food intake using continuous glucose monitoring (CGM) data. A variational Bayesian learning scheme was applied to define the number and values of the system's parameters by iterative optimisation of free energy. The model has the minimal order and number of parameters to successfully describe blood glucose dynamics in people with and without DM. The model accounts for the nonlinearity and stochasticity of the underlying glucose–insulin dynamic process. Being data-driven, it takes full advantage of available CGM data and, at the same time, reflects the intrinsic characteristics of the glucose–insulin system without detailed knowledge of the physiological mechanisms. We have shown that the dynamics of some postprandial blood glucose excursions can be described by a reduced (linear) model, previously seen in the literature. A comprehensive analysis demonstrates that deterministic system parameters belong to different ranges for diabetes and controls. Implications for clinical practice are discussed. This is the first study introducing a continuous data-driven nonlinear stochastic model capable of describing both DM and non-DM profiles.

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1. Introduction

Tight glycaemic control using medication and life style adjustments has proven effective in reducing or delaying complications of DM [1]. There has also been major progress in the development of model predictive control devices, i.e. artificial pancreas systems [2] for type 1 diabetes (T1D), and attempts to automatically control blood glucose variations in people with type 2 diabetes (T2D) [3]. As stated in [2], the vital ingredient of predictive control algorithms is a model that captures the relationship between glucose excursions, food intake and insulin delivery. The development of such a model represents a major challenge due to limited access to quality data, high cost of equipment for data collection, and, most importantly, the complexity of the underlying systems dynamics. The latter includes four major properties: the glucose–insulin system is open, event-driven, nonlinear and stochastic. These essential properties are rarely incorporated altogether into models of blood-glucose dynamics.

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* *Corresponding author.*
E-mail address: n.khovanova@warwick.ac.uk (N. Khovanova).

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One of the reasons is that the inherent system complexity often leads to over-complicated models with large numbers of parameters, unsuitable for practical use. Let us briefly summarise two main types of model available in the literature and highlight the advantages of the approach taken in this work.

Phenomenological models [4–8] describe the underlying physiological process (production, distribution, and degradation of glucose and insulin) by compartments, each of which is associated with several differential equations. Although the inherent nonlinearity of the glucose–insulin interaction has been recognised in these models, their application in predictive control is limited by two factors: they are not person specific and contain a high number of system parameters making such models hard to map to low-dimensional data and to validate [9].

Data-driven models [5,10–13] are able to exploit the information hidden in the data and predict glucose concentration without detailed knowledge of the underlying physiological processes [14]. An accepted challenge of such data-driven models is the interpretation of their parameters. They also categorise every poor fit as measurement noise, without taking stochasticity in the data and uncertainty in the model into consideration. In nonlinear systems, noise acts as a driving force; it can radically modify deterministic dynamics, and therefore clearly requires inclusion in the model. This model uncertainty problem can be addressed using probabilistic identification techniques, which operate with parameter distributions rather than single values, and such an approach is taken in this work.

The aim of this work was to find a parsimonious model formulation, i.e. a model of minimal order and with a minimal number of parameters, for postprandial (after a single food intake) glucose dynamics. The model should account for the essential systems properties listed above, and be suitable to support the control strategies in clinical settings. The framework for our approach lies in the area of *data-driven* nonlinear stochastic differential equations modelling. Data-driven models based on differential rather than difference equations have been explored, e.g. in a single case study [15], and for linear systems [16]. It has been shown [15] that postprandial blood glucose excursions can be modelled by a second order linear differential equation in which food intake is treated as a bolus injection of glucose, i.e. an impulsive force. It has also been demonstrated [17] that such linear systems can successfully describe some postprandial glucose excursions in subjects without DM, whereas a strong nonlinear characteristic of the responses was evident for many DM profiles. This highlights the importance of including nonlinear terms in modelling equations as opposed to linear systems approaches.

The structure of the article is as follows. Section 2 gives details on the data available for the analysis. Section 3 explains the methodology for model formulation. Section 4 presents the model, a detailed analysis of systems parameters for profiles with and without DM, and some clinically related interpretation. Section 5 summarises the results, justifies the need for further work and outlines the relevance of the model for DM management.

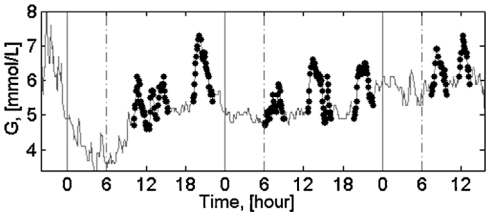

Fig. 1 – Example subcutaneous glucose time series G(t) of a participant from the control group. The solid grey curves represent the measured glucose values and the dots are the values used for modelling of single postprandial peaks. The solid and dashed vertical lines correspond to midnight (0 h) and 6 am, respectively. The first several hours of data (to the left from the first solid vertical line) were excluded from modelling due to the adjustment period of the CGM system.

2. Data description

Datasets from 15 volunteers including five people without DM (control group), four patients with T1D and six patients with T2D was available for the study [17]. Recruitment was purposive to ensure a diverse sample of ages and treatment regimens. Baseline biographical data (Table A.1 in Appendix) were obtained on age, sex, body mass index, type of diabetes, treatment regimen and on recent HbA1c value, indicating the average blood glucose level in the past 2–3 months. Subcutaneous glucose values (Fig. 1) were taken every 5 min over 72 h using the Medtronic Minimed CGM system [18]. No restrictions were placed on usual daily activities of the participants.

The dotted peaks in the time series (Fig. 1) represent the postprandial glucose concentration. To avoid mistaking measurement error for genuine postprandial peaks, only distinguishable peaks with height more than 1.1 mmol/L during daytime from 6 am to midnight were selected. The highest peak value for the participant in the control group is just below 8 mmol/L, whereas the highest values for the T1D and T2D patients are greater than 15 mmol/L (not shown).

3. Model and methods

3.1. *Model formulation*

There are three important characteristics of the blood glucose response to food intake to be taken into account. Firstly, the glucose response is nonlinear as explained in Section 1. Secondly, stochasticity enters into the model in two forms: as measurement error (noise) arising from the device, and/or as dynamical intrinsic noise resulting from factors other than food intake, including physical activity and emotional stress. For patients using insulin, inaccurate estimation of the necessary dose is another factor influencing postprandial excursions. Thirdly, the endocrine system tends to maintain homoeostasis, and any deviations of blood glucose from the basal level decay rapidly and return to the pre-disturbed state. The basal glucose level usually demonstrates slow nonstationary dynamics [17]. On the time scales corresponding to a single peak, the variations are small compared with the changes of

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